Apolipoproteins

Apolipoproteins are proteins that bind to lipids to form lipoproteins, whose main function is to transport lipids. See also the separate Hyperlipidaemia article. Apolipoproteins are important in maintaining the structural integrity and solubility of lipoproteins and play an important role in lipoprotein receptor recognition and the regulation of certain enzymes in lipoprotein metabolism.

There are six major classes of apolipoproteins: A, B, C, D, E and H. Specific apolipoprotein disorders are rare but there is increasing knowledge and awareness of the importance of apolipoproteins and their relevance to a variety of clinical disorders.

Apolipoprotein A (apo A)

Apo A1

- Apo A1 is the major protein component of high-density lipoprotein (HDL).[1] Deficiency of apo A1 is associated with HDL deficiencies, including Tangier disease and systemic non-neuropathic amyloidosis.[2]
- Apo A1 may have a role in protection against Alzheimer's disease.
- Apo A1 and apo E interact to modify triglyceride levels in coronary heart disease patients.

Apo A5

- Apo A5 is a probable biochemical and genetic marker of increased triglyceride concentrations and also a risk factor of coronary disease in some populations.[3]

Apolipoprotein B (apo B)

- Apo B is the main apolipoprotein of chylomicrons and low-density lipoproteins (LDLs).[4] High levels appear related to heart disease.
- Apolipoprotein B and the apo B/apo A1 ratios are thought to be a better marker of risk of vascular disease and a better guide to the adequacy of statin treatment than any cholesterol index.[5] A large study concluded that the non-fasting apo B/apo A1 ratio was superior to any of the cholesterol ratios for estimation of the risk of acute myocardial infarction in all ethnic groups, in both sexes and at all ages.[6]
- Apo B and the apo B/apo A1 ratio have been shown to be predictive of ischaemic stroke in patients with previous transient ischaemic attack.[7]
- However, a previous study found that non-HDL-C and the ratio of total cholesterol to HDL-C were as good as, or better than, apolipoprotein fractions in the prediction of future cardiovascular events.[8]

Abetalipoproteinaemia and hypobetalipoproteinaemia[9]

- Hypobetalipoproteinaemia is a genetic disorder that can be caused by a mutation in the apo B gene; abetalipoproteinaemia is usually caused by a mutation in the microsomal triglyceride transfer protein (MTTP) gene.
- Abetalipoproteinaemia:
    - A rare autosomal recessive disorder that interferes with the normal absorption of fat and fat-soluble vitamins. It is caused by a deficiency of apo B48 and apo B100. Heterozygotes have no symptoms and no evidence of reduced plasma lipid levels.
    - Abetalipoproteinaemia is associated with absent LDL and very low-density lipoprotein (VLDL). Clinical features include fat malabsorption, progressive ataxia (spinocerebellar degeneration), acanthocytic red blood cells and retinitis pigmentosa. Death usually occurs before the age of 30 years.

- Hypobetalipoproteinaemia:
    - Characterised by apo B <5th percentile and low LDL-cholesterol. Over 60 mutations producing truncations in the apo B gene have been identified.[10]
    - Homozygotes present with fat malabsorption and low plasma cholesterol levels at a young age and develop similar clinical features to abetalipoproteinaemia.
    - Heterozygotes are usually asymptomatic but have low LDL cholesterol and apo B levels.
    - Secondary hypobetalipoproteinaemia may occur - eg, with occult malignancy, malnutrition or chronic liver disease.
- Early diagnosis, high-dose vitamin E and medium-chain fatty acid supplements may slow the progression of the neurological abnormalities.

Familial defective apoprotein B100

- Autosomal dominant disorder involving a mutation of apo B that interferes with binding of LDL.
- Total cholesterol and LDL levels are raised; triglyceride levels are normal.
- Clinical presentation is very similar to familial hypercholesterolaemia. It has been estimated that up to 4% of patients with clinical familial hypercholesterolaemia may have familial defective apo B.

Apolipoprotein C (apo C)

Apo C2

- Apo C2 activates lipoprotein lipase in capillaries, liberating fatty acids and monoglycerides from chylomicrons, with the fatty acids then passing into adipocytes or muscle.[11]
- Defective apo C2 production causes hyperlipoproteinaemia type IB, characterised by hypertriglyceridaemia, xanthomas and increased risk of pancreatitis and early atherosclerosis.

Apo C2 deficiency [12]

- Rare autosomal recessive hereditary disorder.
- Apo C2 activates lipoprotein lipase and so there is an overlap between lipoprotein lipase deficiency and apo C2 deficiency.
- Deficiency of apo C2 leads to an accumulation of chylomicrons and triglycerides.
- Xanthomas and hepatosplenomegaly are less common in apo C2 deficiency than in lipoprotein lipase deficiency.
- Diagnosis is by absence of apo C2 on protein electrophoresis.
- Mainstay of treatment is a fat-free diet.

Apo C3

- Apo C3 inhibits lipoprotein lipase and hepatic lipase. Increased apo C3 expression may lead to hypertriglyceridaemia and an atherogenic lipoprotein profile. [13]
- Two susceptibility haplotypes (P2-S2-X1 and P1-S2-X1) have been discovered in apo A1-C3-A4 gene cluster on chromosome 11q23. These confer approximately three-fold higher risk of coronary heart disease.

Serum levels of apo C1 and apo C3 are reduced in patients with stomach cancer and may have a role in the formulation of a diagnostic score for stomach cancer patients. [14]

Apolipoprotein D (apo D)

- Apo D is a component of HDL in human plasma. [15]
- Apo D is also a biomarker of androgen insensitivity syndrome.
- There is increasing evidence for a prominent neuroprotective role of apo D because of its antioxidant and anti-inflammatory activity. [16]

Apolipoprotein E (apo E)

- Apo E is involved in receptor recognition of intermediate-density lipoprotein and chylomicron remnant by the liver. It is essential for the normal catabolism of triglyceride-rich lipoprotein constituents. [17]
- There is thought to be an association between apo E and neurodegenerative conditions such as multiple sclerosis and Alzheimer's disease. [18] [19]
- There is also convincing evidence linking the apo E genotype to risk of cerebral amyloid angiopathy. [20]
- Neonates with brain injuries and/or defects who also have abnormalities in the apo E gene may have an increased risk for cerebral palsy.
- In familial dysbetalipoproteinaemia, increased plasma cholesterol and triglycerides are the consequence of impaired clearance of chylomicron and VLDL remnants because of a defect in apo E. [21]

Apo E2

- Apo E2 is associated with hyperlipoproteinaemia type III.

Apo E4

- Apo E4 has been implicated in atherosclerosis, Alzheimer's disease and impaired cognitive function.
- The E4 variant is the largest known genetic risk factor for early-onset Alzheimer's disease in a variety of ethnic groups. [22]
- Caucasian and Japanese carriers of 2 epsilon 4 alleles have between 10 and 30 times the risk of developing Alzheimer's disease by 75 years of age, as compared with those not carrying any epsilon 4 alleles:
- The genotype most at risk for Alzheimer's disease and at earlier age is apo epsilon 4,4.
- The 3,4 genotype is at increased risk, although not to the degree of those homozygous for apo epsilon 4.

- The genotype 3,3 is considered at normal risk for Alzheimer's disease. People with 2,4, are also at normal risk.
- The genotype 2,3 is considered at less risk for Alzheimer's disease.
- Apo E epsilon 4 is also associated with poor outcome after traumatic brain injury and brain haemorrhage.[20]

Apolipoprotein H (apo H)[23]

- Also called glycoprotein I, beta-2 (B2gp1).
- Apo H has been implicated in a variety of physiological processes, including blood coagulation, haemostasis and the production of antiphospholipid antibodies characteristic of antiphospholipid syndrome.

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Originally Published: 20/11/2023	Next review date: 26/08/2015	Document ID: doc_1523